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News and Perspectives

Hepatitis C Infection and Metabolic Syndrome

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Infection with the Hepatitis C virus (HCV) is a globally important cause of chronic hepatitis, cirrhosis and hepatocellular carcinoma.[1,2] HCV infection is also associated with several extrahepatic manifestations, including mixed cryoglobulinemia, non-Hodgkin lymphoma, porphyria cutanea tarda, lichen planus, thyroid disease (usually hypothyroidism), lymphocytic sialadenitis, and polyarthritis.[3] Among extrahepatic diseases, metabolic derangements of patients with chronic HCV infection have been increasingly recognized and have become an area of active investigation, especially given the global epidemic of obesity and diabetes. Although a direct link between obesity or metabolic syndrome and HCV infection remains unclear,[4] several studies have demonstrated synergistic effects of HCV infection and obesity on the development of liver cancer.[5] Accumulating evidence already demonstrates that HCV infection has an impact on metabolic derangements, including glucose metabolism and lipid metabolism.[6–10] It is thus reasonable to speculate that HCV itself may elicit liver cell damage as well as metabolic abnormalities. Both events will lead to the emergence and progression of metabolic syndrome. The interactions between HCV infection and metabolic syndrome are reviewed and discussed in this article.

HCV Infection and Glucose Metabolism

Epidemiological studies have demonstrated a higher prevalence of HCV infection in diabetic patients compared with matched controls,[6] a higher prevalence of diabetes in HCV-infected patients,[6,8] and an increased risk of developing diabetes in patients infected with HCV than those not infected [relative hazard = 11.58; 95% confidence interval (CI) = 1.39–96.6].[11] Of particular note is that a population-based survey on 10,975 Southern Taiwanese participants identified a significant link between type 2 diabetes mellitus and HCV viremia. The prevalence of type 2 diabetes mellitus in HCV viremic subjects (18.0%) was significantly higher than those in hepatitis B surface antigen (HBsAg)-positive subjects (11.4%) and subjects negative for both viral hepatitis markers (12.5%).[12] Moreover, HCV infection may induce insulin resistance (IR), and this effect seems to be genotype-specific with

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a lower IR in genotype 3 than other genotypes.[13] Our previous studies on Taiwanese chronic hepatitis C patients not only identified an association between higher HCV RNA level and a lower serum adiponectin level, a marker of IR,[14] but also a dose-dependent response between homeostatic model assessment-IR index (a method of IR measurement) and HCV RNA level. [15] These findings have been confirmed by a recent study.[16]

Several mechanisms have been proposed to explain the relationship between HCV infection, IR and diabetes, such as a direct pancreatic β cell destruction, autoimmune β cell injury, and the presence of non-alcoholic fatty liver disease.[17] One study examined the liver specimens from non-obese and non-diabetic subjects with HCV infection and found that HCV infection may contribute to IR by causing an insulin signaling defect in hepatic insulin receptor substrate (IRS)-1 tyrosine phosphorylation and phosphatidylinositol 3-kinase activation.[18] In addition, studies on HCV core-transgenic mice livers and HCV core-transfected human hepatoma cells demonstrated that HCV may regulate glucose metabolism by core-induced suppression of cytokine signal 3 as well as the promotion of proteasomal degradation of IRS-1 and IRS-2 through ubiquitination.[19] Elevated tumor necrosis factor-alpha level with disturbance in tyrosine phosphorylation of IRS-1,[20] or expression of protein phosphatase 2A to dephosphorylate protein kinase B/Akt have also been indicated.[21] Conversely, despite the small sequence divergence of the HCV core proteins of genotypes 3a and 1b, these two proteins appear to interfere with the insulin signaling pathway by different and genotype-specific mechanisms (Figure).[22]

HCV Infection and Lipid Metabolism

Hepatic steatosis is commonly observed in subjects with chronic HCV, occurring in approximately 50% of liver biopsy samples, with a reported range of 30–70%.[8,14,23,24] A comparison study between 317 HCV liver biopsy specimens and 299 hepatitis B viral specimens indicated that large-droplet fat is more likely to be seen in HCV than in hepatitis B viral infection (OR = 2.4; 95% CI = 1.4–4.1), and Mallory body-like material is found only in HCV biopsy specimens (OR = 71.6; 95% CI = 4.4–996.1).[24] Regarding liver histologic data among patients with different HCV genotype infections, genotype 3a infection has a significantly higher prevalence of steatosis.[9,25] In addition, the grade of hepatic steatosis is associated more with HCV RNA level in genotype 3a infection ($r = 0.786$; $p < .001$), but less with body mass index in genotype 1 infection ($r = 0.689$; $p < .001$).[9] However, existing lines of evidence indicate a combination of host and viral effects on steatosis, with the relative importance of each varying with HCV genotype.[26,27] In Taiwan, HCV genotypes 1 and 2 are more rampant than other genotypes, and hepatic steatosis in chronic hepatitis C patients was found to be associated with features of metabolic syndrome, rather than HCV genotype, advanced fibrosis or the response to antiviral therapy.[10] The link between HCV and metabolic abnormalities is further supported by two population-based studies from Taiwan, one showed an association between positive anti-HCV and serum high-density lipoprotein-cholesterol level as well as serum triglyceride level,[28] and the other demonstrated lower serum cholesterol and triglyceride levels in HCV viremic patients.[29] Furthermore, our recent data identified that chronic hepatitis C patients not only have higher high-density lipoprotein-cholesterol, lower total cholesterol, triglyceride, and low-density lipoprotein-cholesterol (LDL) levels, but also higher serum adiponectin levels than matched healthy controls.[7] Conversely, sustained disappearance of HCV is associated with reduction of steatosis in genotype 3,[30] and a correction of baseline low serum cholesterol and LDL.[27,31] A recent study confirmed that HCV infection was associated with decreased cholesterol and LDL levels and this hypolipidemic effect disappeared with successful hepatitis C treatment but persisted in non-responders.[31] Additionally, a significant portion of patients successfully treated had rebound LDL and cholesterol to levels associated with increased risk of coronary heart disease.

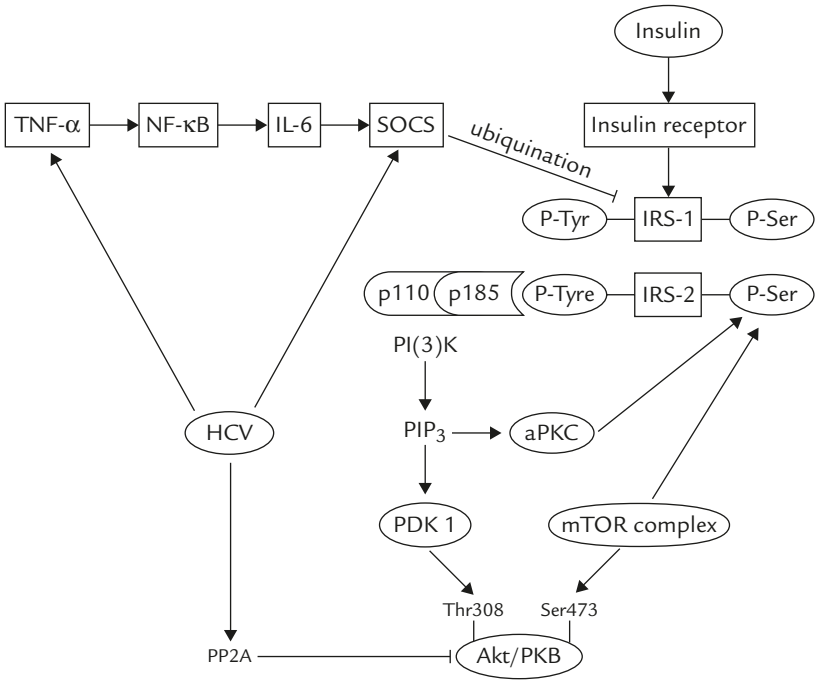

Figure. Hepatitis C virus affects signal transduction of insulin. The insulin receptor is tyrosine kinase-linked and undergoes autophosphorylation. This receptor catalyses the phosphorylation of cellular proteins such as insulin receptor substrate (IRS)-1 or 2. Upon tyrosine phosphorylation, these proteins interact with signaling molecules, resulting in a diverse series of signaling pathways, including activation of phosphatidylinositol-3-OH kinase and downstream PtdIns(3,4,5)P_3-dependent protein kinases (PIP_3-dependent protein kinases), such as phosphoinositide-dependent kinase 1 (PDK1) or atypical protein kinase C. PIP_3 interacts with and activates PDK1, which partially activates protein kinase B (PKB) by phosphorylating PKB at Thr308. Maximal activation of PKB also requires the phosphorylation of Ser473 by mammalian target of rapamycin (mTOR) complex. These pathways act in concert to coordinate the regulation of glucose, lipid and protein metabolism. Hepatitis C virus (HCV) may affect these pathways by core-induced suppression of cytokine signal 3, as well as the promotion of proteasomal degradation of IRS-1 and IRS-2 through ubiquitination. Alternatively, HCV may elevate tumor necrosis factor-alpha (TNF-α) levels disturbing tyrosine phosphorylation of IRS-1, or expression of protein phosphatase 2A (PP2Ac) to dephosphorylate PKB/Akt.

The mechanisms involved in the association of hepatic steatosis with HCV infection remain unclear.[32] Evidence from transgenic murine models showed that expression of HCV structural proteins enhances a low background of hepatic steatosis,[33] and HCV core protein may inhibit microsomal triglyceride transfer protein activity, very low density lipoprotein secretion,[34] as well as alter the expression patterns of lipid metabolism genes.[35] Recent studies further identified the important roles of HCV core and NS5A protein on HCV-induced dyslipidemia and steatosis.[36–39] Moreover, experiments have demonstrated the important roles of assembly and secretion of very low-density lipoproteins in HCV production,[40] and using inhibitors of lipid metabolism may suppress replication of infectious HCV clones.[41] Of particular note, the lipid droplet, an organelle for the storage of neutral lipids, has been linked to the production of infectious virus particles,[42] which implies a linkage between HCV RNA levels and lipid profiles. We thus assessed this possible link in 531 chronic hepatitis C patients, and found a proportional relationship between serum lipid profiles and hepatitis C viral load in patients with genotype 2 infection, but not in genotype 1 infection.[43]

Effects of Metabolic Abnormalities on HCV Infection

In addition to the impact of HCV infection on metabolic profiles, metabolic abnormalities may influence disease progression and therapeutic response in chronic hepatitis C patients. Several

studies have shown a significant and independent association between the grade of steatosis and liver fibrosis,[44] as well as IR and fibrotic progression in chronic hepatitis C.[13] Meanwhile, obesity, defined as a body mass index greater than 30 kg/m^2, is a negative predictor of response to hepatitis C treatment, independent of genotype and cirrhosis.[45] Similarly, a higher IR is associated with a lower sustained virologic response in patients treated with combination therapy of peginterferon plus ribavirin,[46,47] especially among a "difficult-to-treat" population.[48] A study evaluating 198 chronic hepatitis C patients treated with combination therapy showed that HCV genotype 1b virus may induce IR via up-regulation of suppressor of cytokine signal 3 to impair therapeutic response ($OR = 6.7$; $p < 0.005$).[19,49] Conversely, clearance of HCV appears to improve IR, β cell function and hepatic IRS-1/2 expression.[50]

Conclusions

HCV induces several metabolic abnormalities as well as interacts with the components of metabolic syndrome. These interactions vary among different HCV genotypes. In addition, each component of metabolic syndrome can directly influence the other, and thus all components should be managed simultaneously to delay or prevent disease progression and to improve therapeutic response in patients with chronic HCV infection.

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